201-15159A

OVERALL SUMMARY FOR N-METHYL FORMAMIDE

Physical and Chemical Characteristics

N-Methylformamide (also known as monomethylformamide or MMF) is a clear, colorless liquid with a slight amine odor. MMF has a water solubility value of $1.0x10^6$ mg/L, has a melting point of –3.8°C, and boils at 199.5°C. MMF has a vapor pressure of 0.253 mm Hg @ 25°C, density of 0.9961 g/cm^3 @ 25°C, a flash point of 119°C, and flammability limits of 1.8-19.7%. **Data for physical and chemical characteristics are complete and no further testing is recommended.**

Table 1: Physical and Chemical Characteristics for MMF

Melting Point	-3.8°C
Boiling Point	199.5°C
Density	0.9961 g/cm^3 @ 25°C
Vapor Pressure	0.253 mm Hg @ 25°C
Log Kow	-0.97; -1.14
Water Solubility	$1.0x10^6$ mg/L
Flash Point	119°C
Flammability Limits	1.8-19.7%

Environmental Fate

If released to air, a vapor pressure of 0.25 mm Hg @ 25°C indicates MMF will exist solely as a vapor in the ambient atmosphere. Vapor-phase MMF will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 57 hours. If released to soil, MMF is expected to have very high mobility based upon an estimated Koc of 0.0439. Volatilization from moist soil surfaces is not expected to be an important fate process based upon an estimated Henry's Law constant of $2.0x10^{-8}$ atm-m^3/mole. MMF has been shown to biodgrade using microorganisms obtained through soil enrichment. If released into water, MMF is not expected to adsorb to suspended solids and sediment based upon the estimated Koc. MMF, present at 400 mg/L, reached 4%, 98%, and 100% of its theoretical BOD in 3 hours, 3 days, and 7 days, respectively, using an industrial activated sludge inoculum and the Zahn-Wellens test; therefore, MMF is inherently biodegradable and expected to biodegrade in the aquatic environment. Hydrolysis is not expected since amides hydrolyze very slowly under usual environmental conditions. Volatilization from water surfaces is not expected to be an important fate process based upon this compound's estimated Henry's Law constant. An estimated BCF of 3 suggests the potential for bioconcentration in aquatic organisms is low (HSDB, 2003). Consistent with behavior described above and assuming equal emissions to air, water, and soil, any residual MMF is expected to be distributed primarily to water (39.7%) and soil (59.8%) based on the Mackay Level III fugacity model. **No further environmental fate testing is recommended.**

Table 2: Environmental Fate for MMF

Bioaccumulation*	Low potential for bioaccumulation BCF = 3
Biodegradation	Readily biodegradable* 4% ThBOD in 3 hours 98% ThBOD in 3 days 100% ThBOD in 7 days
Fugacity*	Air: 0.43% Water: 39.7% Soil: 59.8% Sediment: 0.073% Based on standard emission scenario: 1000 kg/h for air, water and soil
* Modeled data.	

Ecotoxicology

Existing aquatic toxicity test data can be found in Table 3. Modeling of physical/chemical parameters (i.e., Kow) and aquatic toxicity was conducted to help provide insight into the behavior in the environment and the aquatic toxicity of MMF. Syracuse Research Corporation models for estimating physical/chemical properties were used to estimate $\log_{10}$ Kow (Meylan and Howard, 1995) for subsequent use in the ECOSAR program (Table 1). ECOSAR (Meylan and Howard, 1999) was used to estimate the aquatic toxicity of MMF to green algae, daphnids (planktonic freshwater crustaceans), and fish. ECOSAR predictions are based on actual toxicity test data for classes of compounds with similar modes of action. The existing aquatic toxicity test data and ECOSAR predictions indicate that MMF is likely to be of low concern for acute toxicity to algae, invertebrates, or fish at environmentally relevant concentrations. **No further ecotoxicity testing is recommended.**

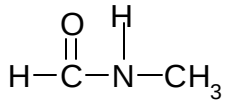
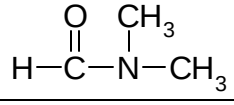
Table 1: Ecotoxicology

	MMF Test Data	**MMF Modeled Data**
Log Kow	No Data	-1.14
Toxicity to Fish (96-hour)	LC_{50} (fathead minnow) > 10,000 mg/L (N) LC_{50} (fathead minnow) > 5,000 mg/L (N)	LC_{50} = 39,170 mg/L (E)
Toxicity to Invertebrates (48-hour)	EC_{50} (*Daphnia*) > 500 mg/L (N)	EC_{50} = 33,787 mg/L (E)
Toxicity to Algae (EC_{50} value for growth inhibition)	72-hr $EC_{10\text{-}90}$ > 8000 mg/L (N)	96-hr EC_{50} = 17,630 mg/L (E)
E = estimated value, N = value based on nominal concentrations.		

Mammalian Toxicology

While reliable MMF data are available to address most of the mammalian toxicology endpoints, certain data are lacking. The available MMF repeated dose study was 2 weeks in duration, rather than the recommended 28-day study. While numerous developmental studies were available, limited data were available regarding reproductive toxicity. With regards to genetic toxicity, an Ames test was available for MMF, but no data on clastogenicity were available. In order to strengthen the mammalian toxicologic database for MMF, supporting data for DMF (a structural analog) are provided.

Table 4: Structural Analogs

Chemical	CAS Number	Structure
N-Methylformamide (MMF)	123-39-7	
Dimethylformamide (DMF)	68-12-2	

DMF is closely structurally related to MMF (see Table 4 above), in that both contain an N-substituted formamide moiety. The substances differ only in the degree of substitution on the nitrogen atom; MMF contains one methyl group and DMF contains two. Review of the toxicologic databases for MMF and DMF indicates that the two substances have generally similar toxicity profiles. For those areas where DMF data is being used as a structural analog to provide supporting data for MMF, detailed robust summaries are provided in this document. In addition, physiochemical properties of DMF are generally similar to MMF and are provided in the detailed robust summary format.

The pathways for biotransformation of DMF and MMF have been extensively investigated. Qualitatively, the pathways of metabolism for DMF and MMF are quite similar. The major pathway for primary metabolism of DMF is the P450-mediated oxidation to form *N*-(hydroxymethyl)- *N*-methylformamide (HMMF). An alternative pathway for biotransformation of DMF is formal demethylation to yield MMF. MMF is further metabolized by hydroxylation of the remaining methyl group to form *N*-(hydroxymethyl) formamide, or by oxidation of the formyl carbon, leading to formation of a reactive carbamoylating intermediate. The reactive intermediate can react with cellular glutathione (GSH) to yield SMG, which is eventually excreted in the urine as the corresponding mercapturic acid. A more detailed discussion of the metabolism of DMF and MMF is presented at the end of the toxicity section.

Mammalian Acute Toxicity

MMF has slight acute oral toxicity with an LD_{50} in rats of 4000 – 7077 mg/kg and an LD_{50} in mice of approximately 2600 mg/kg. MMF was moderately toxic by skin absorption in the pregnant rabbit with an ALD of 1500 mg/kg and exhibited very low toxicity by skin absorption in the pregnant rat with an ALD of 11,000 mg/kg. The ALD studies were conducted in pregnant

rats and rabbits as the dose selection portion of an embryotoxicity study. MMF was irritating to rabbit eyes. No information was available on dermal irritation or sensitization. **No further acute toxicity testing is recommended for MMF.**

Table 5: Mammalian Acute Toxicity

Oral LD_{50}	4000 – 7077 mg/kg (rat) 2600 mg/kg (mice)
4-hour Inhalation ALC	> 10.76 mg/L (rat)
Dermal ALD	11,000 (rat) 1500 (rabbit)
Eye Irritation	Irritating

Repeated Dose Toxicity

The primary target organ in repeated dose studies appears to be the liver for both MMF and DMF. These effects appear at similar doses/exposures to the 2 chemicals. In a two-week inhalation study with MMF, no adverse effects were seen in rats exposed to 50 ppm. Higher concentrations (132 and/or 402 ppm) produced compound-related biochemical and microscopic pathology changes in the liver. Longer term repeated dose studies of MMF were not available; however, data were available on the structurally similar compound, DMF. In a two-week inhalation study in rats with DMF, increased liver weights were observed at 91 ppm. In a 90-day inhalation study with DMF, evidence of hepatocellular injury was seen as early as day 4 on increases in the activities of liver-specific enzymes at concentrations of 200 ppm and above. Relative liver weights were increased in males at 100 ppm and above and in females at 50 ppm and above. Pathologic changes of the liver (minimal to moderate centrilobular hepatocellular necrosis) were observed at 400 ppm and above. **No further repeated dose toxicity testing is recommended.**

Table 6: Repeated Dose Toxicity

	MMF	**DMF**
Two-Week Inhalation Study	NOEL = 50 ppm Pathologic changes in the liver and increased liver weights at 132 and/or 402 ppm.	NOEL < 91 ppm Increased liver weights were observed at 91 ppm.
90-Day Inhalation Study	No Data	NOEL< 50 ppm Biochemical changes in liver enzymes at 200 ppm and above in rats. Increased relative liver weights at 50 ppm and above in rats and mice. Pathologic changes in the liver at 400 ppm and above in rats and 50 ppm and above in mice.

Developmental Toxicity

For both MMF and DMF, the fetus appears to have the same sensitivity to the test chemicals as the maternal animal.

MMF did not produce developmental effects at maternally non-toxic doses when given by inhalation to rats (Rickard et al., 1995), dermally to rats (Stula and Krauss, 1977), and orally to rats (Kelich et al., 1995; Merkle and Zeller, 1980) and rabbits (Kelich et al., 1995). Developmental effects were observed in mice when treated with MMF orally and dermally (Roll and Baer, 1967). The quality of these studies vary, ranging from scientifically rigorous study design and thorough reporting (Kelich et al., 1995; Rickard et al., 1995), to studies with little study design and reporting details (e.g. maternal toxicity not reported or differential toxicity reported with limited study information) (see Section 5.3 for complete listing of studies). In studies in which both maternal and fetal effects were carefully examined (Kelich et al., 1995; Rickard et al., 1995), the effects of MMF appeared at the same dose levels in maternal and fetal animals. In the inhalation study in rats (Rickard et al., 1995), maternal lethality and toxicity was demonstrated at 150 ppm MMF and maternal toxicity remained evident as mild respiratory distress in the 50 ppm treated dams. Decreased fetal weight and fetal malformations and variations were observed at 150 ppm. Developmental toxicity, expressed as slight depression in fetal weight, was evident at 50 ppm. The NOEL for both the dam and the fetus was 15 ppm. In an oral study in rats and rabbits (Kelich et al., 1995), maternal toxicity was evidenced as decreased body weight and food consumption at 75 mg/kg in rats and 50 mg/kg in rabbits. Developmental toxicity was evidenced by reduced fetal viability, reduced fetal weight, and fetal malformations at 75 mg/kg in rats and 50 mg/kg in rabbits. The NOEL for maternal and fetal toxicity was 10 mg/kg in both rats and rabbits.

Extensive testing has been conducted in rats and rabbits by inhalation, oral, and dermal routes of exposure which shows that DMF affects the embryo/fetus only under conditions which will affect the maternal animal. Rats exposed by inhalation to either 18 or 172 ppm during gestation showed no structural changes. Both maternal and fetal weights were reduced at 172 ppm (Kimmerle and Machener, 1975). Similarly, no teratogenic effects were seen in rats inhaling either 30 or 300 ppm during gestation with weights affected in both maternal and fetal rats at 300 ppm (Lewis et al., 1992). Oral studies in rats showed maternal toxicity at doses of 100 mg/kg or greater along with fetal toxicity at the same doses. No malformations were seen and the fetal effect consisted of weight depressions and skeletal developmental delays (Saillenfait et al., 1997). DMF given orally to rabbits produced both maternal and fetal effects with fetal anomalies being produced at doses that had little maternal effect (Merkle and Zeller, 1980). Studies in other species and those involving dermal exposure supports the hypothesis that the maternal and fetal animals are equally sensitive to the toxic effects of DMF (Kennedy, 1986; 2001). **No further developmental toxicity testing is recommended.**

Table 7: Developmental Toxicity

	MMF	**DMF**
Inhalation Study in rats	Maternal and fetal NOEL = 15 ppm	Maternal and fetal NOEL = 18 ppm Maternal and fetal NOEL = 30 ppm
Oral Study in rats	Maternal and fetal NOEL = 10 mg/kg	Maternal and fetal NOEL = 50 mg/kg
Oral Study in rabbits	Maternal and fetal NOEL = 10 mg/kg	Maternal NOEL = 65 mg/kg Fetal NOEL = 44.1 mg/kg

Reproductive Toxicity

No formal reproductive toxicity studies have been conducted on MMF. Data were available on the structurally similar compound, DMF. Rats given dermal applications of either 500, 1000, or 2000 mg/kg of DMF from 4 weeks pre-mating through the production and lactation of 1 litter showed no effects on reproductive endpoints. Administration of 2000 mg/kg resulted in a reduction in the number of viable pups per litter. Body weight effects were seen in the parents at 1000 and 2000 mg/kg. Fetal and weanling body weights were similar to controls. In a continuous breeding study in which mice were exposed to either 1000, 4000, or 7000 ppm of DMF in their drinking water, a decrease in fertility (reflected by a decrease in pups born alive and in live litter size) was seen at 4000 and 7000 ppm. Liver damage was produced in all parental animals (1000 to 7000 ppm) and body weight gains were affected at 4000 and 7000 ppm. Decreased fertility and fetal effects (decreased pup weight) paralleled the parental sensitivity observed at 4000 and 7000 ppm. No effects on fertility or fetal parameters were observed at 1000 ppm. In a 90-day inhalation study conducted in rats and mice, relative testes weights were increased at 400 ppm and above in the rats; however, no microscopic findings or adverse effects on sperm density or motility were observed in rats or mice. DMF is not considered a unique reproductive toxicant (any reproductive effects have been shown to occur at higher doses/exposures than hepatotoxic effects). Based on its structural similarity and its

similar toxicity profile for developmental and repeated dose toxicity, we expect MMF to not be a reproductive toxin. **No reproductive testing is recommended for MMF.**

Table 8: Reproductive Toxicity

	MMF	**DMF**
Reproductive Toxicity	No Data	Not a unique reproductive toxin* in a 1-generation study or a continuous breeding study
* = reproductive effects have been shown to occur at higher doses/exposures than hepatotoxic effects		

Genetic Toxicity

MMF was not mutagenic in *Escherichia coli*. No data on the clastogenicity of MMF are available. However the genetic toxicity of the analog, DMF, has been extensively investigated. A review of the available literature indicates that although some positive findings have been observed, DMF does not induce chromosome aberrations or gene mutations in most of the systems tested. In *in vitro* bacterial mutation assays, 33/37 tests with DMF produced negative results. DMF was also negative in 14/14 unscheduled DNA synthesis assays (*in vitro*), negative in 19/22 clastogenicity assays (*in vitro*), negative in 8/9 *in vivo* micronucleus assays, negative in 11/11 *in vivo* dominant lethal tests, and negative in 17/17 other *in vivo* genetic toxicity assays. The weight of evidence suggests that DMF and, by analogy, MMF are not genotoxic. **No further genotoxicity testing is recommended for MMF.**

Table 9: GeneticToxicity

	MMF	**DMF**
Mutagenicity	Not mutagenic	Not mutagenic
Clastogenicity	No Data	Not clastogenic

Metabolism

The pathways for biotransformation of N,N-dimethylformamide (DMF) and N-methylformamide (MMF) have been the subject of extensive investigation for over 30 years. The primary driver behind this effort has been the realization that the toxicity of these compounds is intrinsically related to their metabolism, both quantitatively and qualitatively. The primary pathways for biotransformation of DMF and MMF are illustrated in Figure 1. The major pathway for primary metabolism of DMF in all species studies, including humans, is the P450-mediated oxidation of one of the *N*-methyl moieties to form the stable carbinolamide *N*-(hydroxymethyl)-*N*-methylformamide (HMMF, pathway 1) (Gescher, 1993; Van den Bulcke et al., 1994; Hundley et al., 1993a; 1993b; Lareo and Perbelline, 1995). Several lines of evidence indicate that CYP2E1 is the major catalyst for this reaction (Mráz et al., 1993). HMMF is readily excreted in the urine, accounting for approximately 50% of the administered dose of DMF in rats and 22% of the dose in human volunteers exposed by inhalation (Van den Bulcke et al., 1994; Mráz and Nohova, 1992). An alternative pathway for biotransformation of DMF involves formal demethylation to

yield MMF (pathway 2). Demethylation of DMF to MMF is thought to occur both directly (Scailteur and Lauwerys, 1984) and via hydrolysis of HMMF (pathway 2a) (Van den Bulcke et al., 1994).

MMF thus formed is further metabolized by two distinct pathways. The first pathway involves hydroxylation of the remaining methyl group to form *N*-(hydroxymethyl)formamide (HMF, pathway 4), analogous to the oxidation of DMF to HMMF (Kestell et al., 1985; Tupil and Timbrell, 1988). Urinary HMF accounted for approximately 3-6% and 7-9% of the administered dose of MMF in rats and mice, respectively. HMF has not been quantified following administration of DMF, but approximately 13% of the administered dose of DMF in a study involving human volunteers was recovered in the urine as formamide, most of which was thought to result from thermal decomposition of HMF in the analytical system (Mráz and Nohova, 1992). By analogy with HMMF, a small amount of MMF is thought to undergo demethylation to formamide, presumable involving the intermediacy of HMF (pathway 5) (Kestell et al., 1985). The second pathway for further metabolism of MMF is oxidation of the formyl carbon (pathway 3), leading to formation of a highly reactive intermediate thought to play a pivotal role in toxicity of both DMF and MMF. This reaction appears to be catalyzed primarily, if not exclusively, by CYP2E1 (Mráz et al., 1993; Chieli et al., 1995). The existence of this intermediate has been inferred from the detection of *S*-(*N*-methylcarbamoyl)glutathione (SMG) and *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine (AMMC). The metabolite generated by oxidation of the formyl moiety has not been unequivocally identified, but methyisocyanate has been proposed as a likely candidate, as shown in figure 1 (Gescher, 1993). However, other intermediates such as *N*-methylcarbamic acid have not been ruled out (Gescher, 1993; Kestell et al., 1985). There is some evidence to suggest that HMMF may also be oxidized at the formyl carbon, generating the reactive intermediate following hydrolysis of the *N*-hydroxymethyl group (pathway 3), though this route can at most account for ~5% of the total carbamoylating intermediate (Van den Bulcke et al., 1994; Mráz et al., 1993). As indicated in Figure 1, the reactive intermediate can participate in covalent binding to proteins and transcarbamoylation reactions, and is thought to be directly responsible for hepatotoxicity of both DMF and MMF. The carbamoylating intermediate can react with cellular glutathione (GSH) to yield SMG (pathway 6), which has been detected as a biliary metabolite of DMF and MMF (Gescher, 1993). SMG proceeds through the mercapturic acid pathway (pathway 7), and is eventually excreted in the urine as AMMC. Quantitation of urinary AMMC has been proposed as a useful biomarker for occupational exposure to DMF (Lareo and Perbellini, 1995; Sakai et al., 1995). Human volunteers exposed to 30 mg/m^3 DMF excreted approximately 13% of the dose as AMMC (Mráz and Nohova, 1992). As indicated previously, the formation of SMG is reversible, and this metabolite can be hydrolyzed to form methylamine, as could AMMC. Alternatively, methylamine could be formed by direct hydrolysis, or decomposition of the carbamoylating intermediate (pathway 8). The involvement of the reactive intermediate in methylamine formation has been inferred from the prominent kinetic deuterium isotope effect on methylamine formation observed following carbamoyl-^{2}H-MMF in mice (Threadgill et al., 1987).

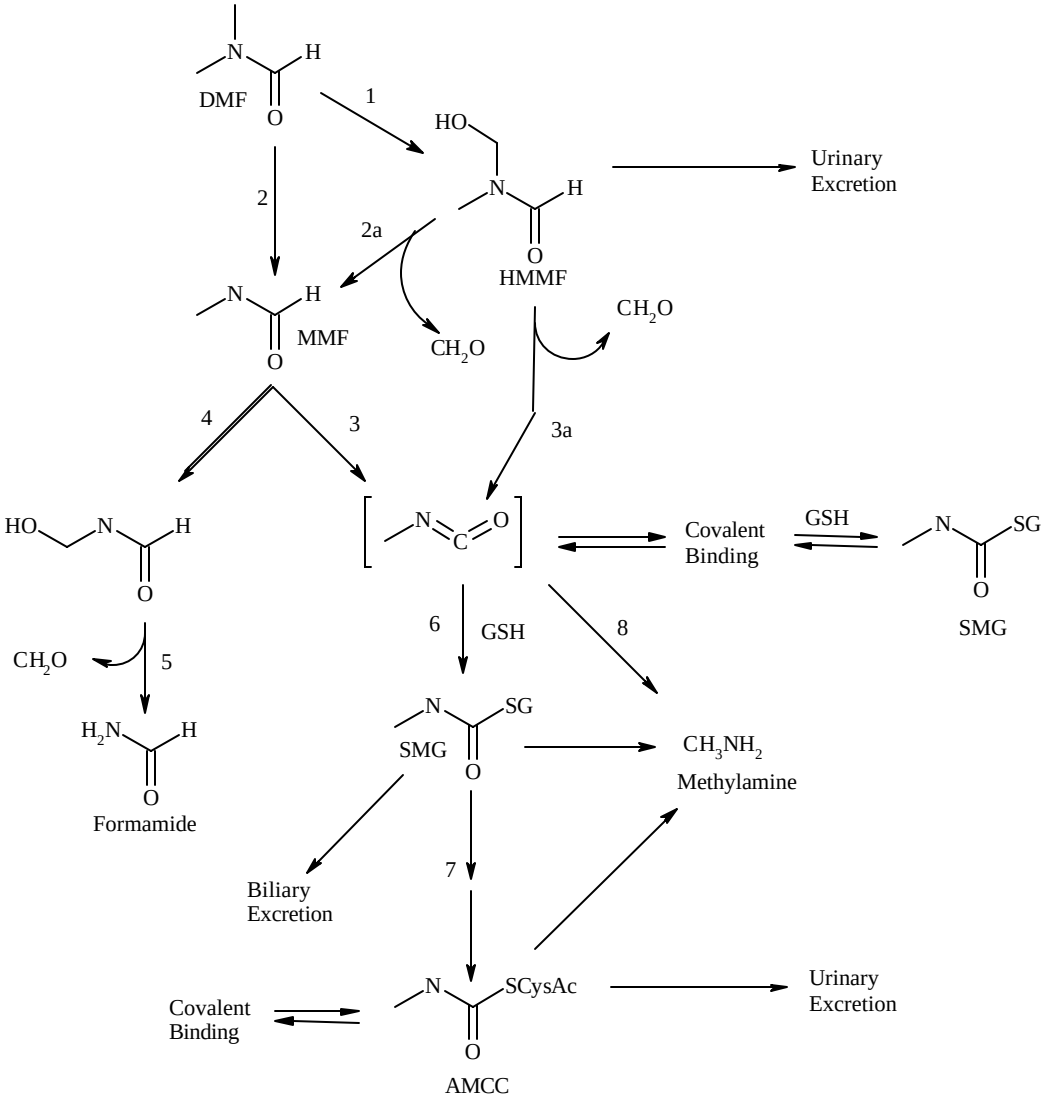
Pharmacokinetic studies of DMF in various species have demonstrated that the area under the plasma concentration vs. time curves (AUC) for DMF increases in the order monkey < mouse < rat following inhalation exposure to comparable concentrations (Hundley et al., 1993a; 1993b). Further, the AUC was found to increase out of proportion with increased exposure concentration,

suggesting saturation of DMF metabolism in all thee species. In all species, the major urinary metabolite was HMMF, followed by DMF and MMF (Hundley et al., 1993a; 1993b). AMMC was not measured in these studies. Comparative excretion studies of DMF in rodents and humans have demonstrated significant quantitative differences in urinary metabolite profiles following i.p. (rodents) or inhalation (humans) exposure (Mráz et al., 1989). In this study, only minute concentration of DMF were detected. Differences in the proportion of the dose excreted unchanged between this and other (Hundley et al., 1993a) studies may be due in part to differences in the route of administration. Excretion of HMMF was greatest in rats (36.8%, followed by humans (25.9%) and mice (8.4%). Formamide (representing formamide + HMF) accounted for 23-38% of the dose in rodents and approximately 14% of the dose in humans. Approximately 1.6-5.2% of the dose was excreted at AMMC in rodents, while humans excreted an average of 14.2% of the dose as AMMC. Following exposure to DMF, excretion of HMMF and MMF are rapid, while excretion of AMMC is delayed, particularly in humans (Mráz and Nohova, 1992). In rodents, hepatotoxicity of DMF is delayed at higher doses compared to lower doses, and this is though to result from the inhibition of metabolism of MMF to reactive species by DMF. Consistent with this idea is the finding that the K_M value for metabolism of MMF to SMG is approximately 20 fold higher than the K_M for metabolism of DMF to HMMF (Mráz et al., 1993). Further, both the metabolism and the hepatotoxicity of MMF were delayed in rats treated simultaneously with DMF (Van den Bulcke et al., 1994; Lundberg et al., 1983). In addition, DMF induces its own metabolism in mice and rats, with lower plasma AUCs observed following repeated exposure compared to single exposure (Hundley et al., 1993a). This effect was not observed in monkeys exposed repeatedly to DMF by inhalation (Hundley et al., 1993b). However, there was a shift in the balance of urinary metabolites in male monkeys, suggesting slightly greater metabolism of DMF to HNNF and MMF following repeated exposure.

In mice, the plasma half-life of MMF administered by *i.p.* injection was approximately 3.6 hours (Gescher et al., 1982). When MMF was administered to rats and mice, a significant fraction of the administered dose was excreted as unchanged MMF in the urine (Tupil and Timbrell, 1988). Excretion of unchanged MMF was greater in rats (23-40%) than in mice (10-12%). In mice, methylamine was the major urinary metabolite (~30% of the dose), whereas this was a comparatively minor metabolite in rats (<10%). Approximately 3-6% of the administered dose was excreted as AMMC in both species. In mice, greater than 90% of the AMMC was excreted within the first 24 hours after dosing with MMF. However, in rats, only about 35% of the total AMMC was excreted in the first 24 hours, with the remainder excreted between 24 and 48 hours. These data are consistent with the generally more rapid metabolism of MMF and greater severity of hepatotoxicity in mice compared to rats, and suggest that the rat may be a more appropriate model for MMF toxicity than the mouse.

Overall, the pathways of metabolism for DMF and MMF are qualitatively similar. Hepatotoxicity of both compounds is thought to be mediated by a reactive carbamoylating intermediate formed by oxidation of the formyl carbon of MMF. Consequently, the hepatotoxicity of the two compounds is qualitatively similar. However, due to inhibition of formyl oxidation step by DMF itself, the hepatotoxicity of the latter compound is delayed with respect to time of exposure.

Figure 1. Metabolic Pathways for Dimethylformamide (DMF) and N-Methylformamide (MMF)



Human Exposure

The predominant use (greater than 95%) of monomethylformamide (MMF) is as a DuPont-limited intermediate. Less than 5% of DuPont's production is sold to external customers. These customers, located in Europe and Japan, use MMF for industrial purposes only: as a solvent in electronics manufacture and as a solvent for chemical synthesis of resins. Personal protective equipment and ventilation are used at these sites to minimize worker exposure.

For the major use, MMF is manufactured at one DuPont plant and is shipped by railcar to another DuPont facility for use as a raw material. MMF is catalytically converted *in-situ* to

another substance, which is then further reacted to form downstream products at the site. The manufacture and use are closed system operations. The only potential human exposure occurs during loading and unloading.

Monomethylformamide is made on a campaign basis twice a year. Monomethylformamide is produced in a closed system and is hard piped to loading spots. Flex hose is connected to the liquid valve on the tank car and the liquid is fed through an induction pipe to the bottom of car. The dome lid is kept down except during periods when operators are performing level checks and collecting samples. Off-gases associated with the MMF process are vented to a flare stack. MMF is shipped by rail to the DuPont use site and is unloaded into a storage tank and is consumed throughout the year. At the DuPont use site, MMF is handled in a closed system except when piping connections are made during the unloading process. A nitrogen pad is kept on the railcar during the unloading process and any vented material goes directly to an incinerator. All transfers from the storage tank and subsequent consumption in the reactor occur under closed system conditions, without exposure to workers.

At the DuPont manufacturing site, potential for employee exposure is greatest when operators perform periodic checks on top of MMF railcars to inspect the dome, do level checks, and collect samples. Operators wear appropriate personal protective equipment (PPE) to protect themselves from liquid and vapor contact while on the railcar. PPE consists of a positive pressure air supplied respirator, Nomex coveralls, and neoprene gloves. Safety showers, eyewash stations, and self-contained breathing apparatus (SCBA) are available in close proximity to the operations area. Chemical splash goggles, Nomex coveralls and neoprene gloves are required by all personnel for patrol-type work during the production of MMF.

At the DuPont use site, employee potential for exposure occurs only during unloading operations. When making connections to lines containing MMF, chemical suit, boots, NIOSH approved hood respirator, and gloves are worn. Chemical gloves, chemical jacket, chemical splash goggles, and faceshield are required for sampling activities involving MMF.

The DuPont Acceptable Exposure Limit (AEL) for monomethylformamide is 2 ppm as an 8- and 12-hour TWA (time-weighted average). Air monitoring has been conducted on monomethylformamide and all measured concentrations are well below the AEL. Results are shown in the table below:

(March 30, 2004)

Exposure Data:

Job Sampled	No. of Results	Average (ppm)	Minimum (ppm)	Maximum (ppm)
DuPont Manufacturing Site Operators (full shift)	**18**	**<0.1**	**<0.1**	**<0.1**
DuPont Manufacturing Site Loaders	**18**	**0.162**	**<0.1**	**0.6**
DuPont Use Site Unloaders (full shift)	**13**		**All <0.1**	

Conclusion

Adequate data are available to address all the required endpoints. A substantial body of data exists for MMF *per se*. Where data are lacking on MMF, reliable data are available for the close analog, DMF. The use of DMF data to supplement the existing mammalian toxicity data for MMF is supported by the close similarity in molecular structure, similarity in physical/chemical properties, and the similarity in toxicity observed where data for both substances are available for comparison. Further strong support for use of DMF as an analog for MMF is provided by the extensive understanding of the metabolic fate of DMF and MMF, and the fact that MMF is one of the products of metabolism of DMF. The use of DMF as an analog to MMF is consistent with the Agency's directive to HPV participants to maximize the use of scientifically appropriate data for related chemicals. Although some differences between MMF and DMF may be expected, we believe these differences to be minimal and insufficient to warrant additional animal testing.

TEST PLAN FOR N-METHYL FORMAMIDE

N-Methyl formamide **CAS No. 123-39-7**	**Data Available**	**Data Acceptable**	**Testing Required**
Study	**Y/N**	**Y/N**	**Y/N**
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y*	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y*	Y	N
Genetic Toxicity Gene Mutations	Y*	Y	N
Genetic Toxicity Chromosomal Aberrations	Y*	Y	N
Y = yes; N= no; NR = not required * = Data are available on an analog chemical.			

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